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12. ☐ Amendments to the claims of the International Application **under PCT Article 19 (35 U.S.C. 371(c)(3)), i.e., before 18th month from first priority date above in item 3, are transmitted herewith (file only if in English) including:**

13. ☒ PCT Article 19 claim amendments (if any) have been transmitted by the International Bureau

14. ☐ Translation of the amendments to the claims **under PCT Article 19 (35 U.S.C. 371(c)(3)), i.e., of claim amendments** made before 18th month, **is attached (required by 20th month from the date in item 3 if box 4(a) above is X'd, or 30th month if box 4(b) is X'd, or else amendments will be considered canceled).**

15. **A declaration of the inventor** (35 U.S.C. 371(c)(4))
a. ☐ is submitted herewith ☐ Original ☐ Facsimile/Copy
b. ☒ is not herewith, but will be filed when required by the forthcoming PTO Missing Requirements Notice per Rule 494(c) if box 4(a) is X'd or Rule 495(c) if box 4(b) is X'd.

16. **An International Search Report (ISR):**
a. Was prepared by ☒ European Patent Office ☐ Japanese Patent Office ☐ Other
b. ☒ has been transmitted by the international Bureau to PTO.
c. ☒ copy herewith (3 pg(s).) ☒ plus Annex of family members (1 pg(s).).

17. **International Preliminary Examination Report** (IPER):
a. ☒ has been transmitted (if this letter is filed after 28 months from date in item 3) in English by the International Bureau with Annexes (if any) in original language.
b. ☒ copy herewith in English.
c.1 ☐ IPER Annex(es) in original language ("Annexes" are amendments made to claims/spec/drawings during Examination) including attached amended:
c.2 ☐ Specification/claim pages #_____ claims #
Dwg Sheets #
d. ☐ Translation of Annex(es) to IPER **(required by 30th month due date, or else annexed amendments will be considered canceled).**

18. **Information Disclosure Statement** including:
a. ☒ Attached Form PTO-1449 listing documents
b. ☐ Attached copies of documents listed on Form PTO-1449
c. ☒ A concise explanation of relevance of ISR references is given in the ISR.

19. ☐ **Assignment** document and Cover Sheet for recording are attached. Please mail the recorded assignment document back to the person whose signature, name and address appear at the end of this letter.

20. ☐ Copy of Power to IA agent.

21. ☐ **Drawings** (complete only if 8d or 10a(4) not completed): ___ sheet(s) per set: ☐ 1 set informal; ☐ Formal of size ☐ A4 ☐ 11"

22. Small Entity Status ⌀ ☐ is **Not** claimed ☒ is claimed (**pre**-filing confirmation required)
22(a) _____ (No.) Small Entity Statement(s) enclosed (since 9/8/00 Small Entity Statements(s) not essential to make claim)

23. **Priority** is hereby claimed under 35 U.S.C. 119/365 based on the priority claim and the certified copy, both filed in the International Application during the international stage based on the filing in (country) United States of:

	Application No.	Filing Date		Application No.	Filing Date
(1)	60/146,978	August 3, 1999	(2)		
(3)			(4)		
(5)			(6)		

a. ☒ See Form PCT/IB/304 sent to US/DO with copy of priority documents. If copy has not been received, please proceed promptly to obtain same from the IB.
b. ☐ Copy of Form PCT/IB/304 attached.

24. Attached: 1) Petition for Revival of an Application for Patent Abandoned Unintentionally Under 37 CFR 1.137(b); 2) Certificate of Express Mailing; and 3) two reply postcards.

RE: USA National Filing of PCT/ /

JC11 Rec'd PCT/PTO 12 FEB 2002

25 Per Item 17.c2, **cancel original** pages #_____, claims #_____, Drawing Sheets #

26. **Calculation of the U.S. National Fee (35 U.S.C. 371 (c)(1)) and other fees is as follows:**
Based on amended claim(s) per above item(s) ☐ 12, ☐ 14, ☐ 17, ☐ 25, ☐ 25.5 (hilite)

Total Effective Claims	34	minus 20 =	14	x $18/$9	=	$126	966/967
Independent Claims	2	minus 3 =	0	x $84/$42	=	$0	964/965
If any proper (ignore improper) Multiple Dependent claim is present,				add$280/$140		+0	968/969

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(4)): ➔➔ **BASIC FEE REQUIRED, NOW** ➔➔➔➔

A. If country code letters in item 1 are **not** "US","BR","BB","TT","MX","IL" "NZ", "IN" or "ZA"

See item 16 re:

1. Search Report was not prepared by EPO or JPO - - - - - - - - - add$1,040/$520 960/961
2. Search Report was prepared by EPO or JPO - - - - - - - - - - - - add$890/$445 +0 970/971

SKIP B, C, D AND E UNLESS country code letters in item 1 are "US","BR","BB","TT","MX","IL", "NZ", "IN", "ZA", "LC" or "PH"

(X) ➔ ☐ B. If USPTO did not issue both International Search Report (ISR) and (if box 4(b) above is X'd) the International Examination Report (IPER), - - - - - - - - - - - - - - - - - - - add$1,040/$520 +0 960/961

(only) (one) ➔ (of) ☐ C. If USPTO issued ISR but not IPER (or box 4(a) above is X'd), - add$740/$370 +0 958/959

(these) (4) ➔ (boxes) ☐ D. If USPTO issued IPER but IPER Sec. V boxes not all 3 YES, - add$710/$355 +0 956/957

➔ ☒ E. If international preliminary examination fee was paid to USPTO and Rules 492(a)(4) and 496(b) satisfied (in IPER Sec. V all 3 boxes must be YES for all claims), - - - - - - add $100/$50 +50 962/963

27. **SUBTOTAL =** $176

28. If Assignment box 19 above is X'd, add Assignment Recording fee of ----$40 +0 (581)

29. If box 15a is x'd, determine whether inventorship on Declaration is different than in international stage. If yes, add (per Rule 497(d) ----$130 +0 (098)

30. Attached is a check to cover the - **TOTAL FEES** $176

Our Deposit Account No. 03-3975
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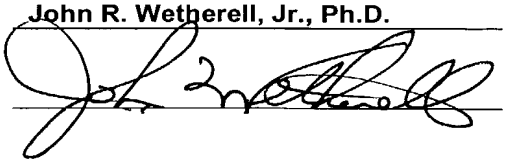
Pillsbury Winthrop LLP
Intellectual Property Group

Carmel Valley Centre I
11975 El Camino Real, Suite 200San
Diego, CA 92130-2593
Tel: (619) 234-5000

Atty/Sec: JRW/lga

By Atty: John R. Wetherell, Jr., Ph.D. **Reg. No.** 31,678

Sig: 

Fax: (858) 509-4010
Tel: (858) 509-4022

NOTE: File in duplicate with 2 postcard receipts (PAT-103) & attachment

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

Inventor(s): Carl M. Andersson, Magnus Gustafsson and Kent Roger I. Olsson

Filed: Herewith

Title: SOLID PHASE PARALLEL SYNTHESIS OF TERTIARY AMINES

February 11, 2002

PRELIMINARY AMENDMENT

Hon. Commissioner of Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

IN THE SPECIFICATION:

At the top of the first page, just under the title, insert

☒ --This application is the National Phase of International Application PCT/US00/21255 filed 03 August 2000 which designated the U.S. and that International Application

☒ was ☐ was not published under PCT Article 21(2) in English.--

Respectfully submitted,

PILLSBURY WINTHROP LLP
Intellectual Property Group

By: _____

Attorney: John R. Wetherell, Jr.
Reg. No: 31,678
Tel. No.: (858) 509-4022
Fax No.: (415) 983-1200

Atty\Sec. JRW/lga

Solid Phase Parallel Synthesis of Tertiary Amines

This application claims priority from U.S. Provisional Application 60/146,978, filed August 3, 1999, which application is incorporated herein by reference.

Field of the Invention

The present invention relates to the synthesis of tertiary amines. More particularly a method of solid phase tertiary amine synthesis through sequential, exhaustive alkylation of a hydroxylamine derivative and cleavage of the N-O bond is described.

Background of the Invention

Solid phase organic synthesis (SPOS) offers considerable advantages compared to traditional solution phase reactions. In particular, solid phase reactions are very attractive for combinatorial and parallel work because of the relative ease of purification of the resin bound material after each reaction step. Purification can be performed by simple washing and filtration. (see e.g., Obrecht and Villalgordo: Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries, Pergamon, 1998).

Since virtually every endogenous and synthetic ligand that interacts with receptors in the central nervous system contains a basic functionality, most often a tertiary or secondary amino group, SPOS methods for the preparation of such compounds remains an extremely important aspect of medicinal chemistry aimed at central nervous system active drugs.

The solid phase organic synthesis of tertiary amines, using the nitrogen as the point of attachment to the solid support, is known in the art. (See Figure 1) However, the methods

described in previous work have disadvantages related to the lability of the linkers used as well as the release reactions.

Summary of the Invention.

Described is a new method for the solid phase synthesis of amines which comprises the linkage of an amino group via an N-O bond from resin-(linker)-O-NH_2. A series of reliable reactions are used for the introduction of all three R groups of the tertiary amine $NR^1R^2R^3$ (forming resin-(linker) O-$N^+R^1R^2R^3$). Finally, a novel release reaction, which delivers exclusively the material that has successfully undergone each of the previous synthetic steps, is performed. (Resin-linker-O-N^+ $R^1R^2R^3$ gives N $R^1R^2R^3$). This type of release reaction, conditional release, serves to provide very pure product without any need for purification. The protocol is equally adaptable to split synthesis or linear parallel synthesis.

Brief Description of the Drawings

The present invention may be better understood by reference to the appended figures and specification.

Figure 1 illustrates the prior art conditional release reaction.

Figure 2 illustrates the prior art alkylation reaction using alkoxyamine.

Figure 3 illustrates alkoxyammonium ion cleavage

Figure 4 illustrates alkoxyammonium ion reactivity in the prior art.

Figure 5 illustrates reductive alkylation and alkylation as used in the prior art.

Figure 6 illustrates the formation of a hydroxylamine resin

Figure 7 illustrates the entire process of the presently described method.

Figure 8 illustrates the novel conditional release reaction.

Detailed Description of the Invention.

Hydroxylamine resin may be prepared according to Salvino et al., or by attachment of a suitably protected hydroxylamine derivative to the desired resin, e. g. chloromethylated polystyrene or polystyrene grafted or functionalized with a suitable linker.

Introduction of the first R-group to the hydroxylamine resin is achieved either via alkylation or oxime formation followed by reduction. R may be any organyl group. More preferably R can be any cyclic, aromatic or acyclic organyl group

Alkylation is performed by reacting the hydroxylamine derivative with an alkylating agent. Suitable alkylating agents are compounds carrying a nucleofuge such as organyl halides, tosylates or the like. In general alkylating agents may have the formula R-LG, wherein R is an organyl and LG is a nucleofuge

In an alternative to alkylation, oxime formation can be run in one pot or the oxime may be isolated. Aromatic groups may be introduced, e.g., via palladium-catalyzed coupling between the resin and an aromatic or heteroaromatic halide or triflate. Any ketone or aldehyde serves to form an oxime with the resin. Many reducing agents can be used to reduce the oxime to the N-substituted hydroxylamine, including aluminum or boron complex hydrides.

The second R-group may again be any organyl group, and may be introduced via alkylation as described above. Alternately reductive amination may be used to introduce the second R group, wherein any aldehyde or ketone together with a suitable reducing agent is used.

The resin bound N,N-dialkylhydroxylamine derivative so obtained may be alkylated with any organic compound carrying a suitable nucleofuge, such as triflate, halide or tosylate, to form the cationic alkoxyammonium intermediate. This step introduces the third R-group.

Every step in the above sequence is easily driven to completion by the use of excess reagents and reactants and subsequent washing of the resin bound intermediate. Very high selectivity for the introduction of precisely one organyl group in each step (avoiding dialkylation) is achieved particularly effectively by performing oxime formation for the introduction of the first R-group, reduction, reductive amination for the introduction of the second R-group and alkylation for the introduction of the third R-group. This sequence of steps is preferred.

Extremely mild and exclusively conditional release is performed by treating the alkoxyammonium resin which has resulted from the above listed steps, with lithium iodide, preferably at elevated temperature. This reaction has been previously performed in solution by Liguori et al. However, the application of this very mild method for cleaving the N-O bond and thus releasing the desired organic product from the polymer support is novel, and serves to release selectively only material that has reacted in all the previous steps.

Furthermore, this method of release is tolerant to the presence of virtually any substituent in the product amine, since only modest temperatures and neutral conditions are used. Removal of the reagent lithium iodide can be performed by liquid-liquid or liquid-solid extraction, optionally in combination with further purification of the organic product $NR''Alk^1Alk^2$ via capture on acidic ion exchange resin, washing, and release as has been described by others. It is noticeable that this new linking strategy shows unprecedented selectivity for the release of only desired material, allows very mild conditions for

assembly and cleavage of the amines and does not leave any compulsory functionality in the product; hence the linking is traceless.

The term organyl is used to denote any acyclic, alicyclic or heterocyclic, alkyl, alkenyl or alkynyl group, or an aromatic or heteroaromatic group. These groups may be branched or unbranched and may be optionally substituted with heteroatom-containing fragments, connected through either a heteroatom or a carbon atom.

A preferred embodiment of the inventive method disclosed comprises the following steps. Initially the hydroxylamine derivative $PONH_2$ is reacted with an alkylating agent having the formula R-LG or with a carbonyl compound having the formula RCOR' to form an oxime intermediate having the formula PON=CR'R. Most preferably the hydroxylamine derivative is reacted with a aldehyde or ketone. The resulting oxime intermediate is reacted with a reducing agent to produce an alkylated derivative, having the formula $PONH(Alk^1)$. The alkylated derivative is reacted with an alkylating agent having the formula R-LG or a carbonyl compound having the formula RCOR' in the presence of a reducing agent to produce a dialkylated derivative having the formula $PON(Alk^1)(Alk^2)$. Most preferably the alkylated derivative is reacted with a carbonyl compound. Even more preferably the carbonyl compound is an aldehyde or a ketone. The resultant dialkylated derivative is reacted with an alkylating agent having the formula R"-X to produce a quaternized derivative, having the formula $PON^+R"(Alk^1)(Alk^2)$. Finally the quaternized derivative is reacted with a reagent which causes cleavage of the O-N bond to produce a tertiary amine having the formula $NR"(Alk^1)(Alk^2)$. In this preferred embodiment of the method P is an organyl group or solid support, R is an organyl group, LG is a nucleofuge, R' is an organyl group or hydrogen, X is a nucleofuge, R" is an organyl group and Alk^1 and

Alk^2 are the same or different and are each independently selected from the group consisting of R and CHRR'.

Examples

The examples given below are not intended to be limiting. Several modifications to the procedures described below are possible. The scope of the invention is limited by the appended claims only.

Examples are given below for the preparation of tertiary amines according to the method of the invention. The stepwise procedure is best exemplified by examples where the hydroxylamine derivative is soluble, i.e. P of the starting $PONH_2$ is an organyl group, since intermediates may be characterized in this case. In the solution phase examples below, P is benzyl. In the solid phase examples below, P is a modified Wang ., Argogel, or Merrifield resin. During the latter experiments, reaction progress was monitored by solid-phase or gel-phase IR spectroscopy.

The methods and reagents employed for cleavage of the quaternized substrates PON^+R_3 are anticipated in the prior art, particularly in Liguori et. al. Chem. Ber. 1988, 121, 105-109 and in Liguori et. al. Tetrahedron 1984, 40, 1901-1906 and references cited therein. Methods for conducting other steps of the invention were also previously described in the art, for example in Swayze et. al. Synlett 1997, 859, Cannon et. al. J. Med. Chem. 1973, 16, 287, and Kano et. al. Tetrahedron 1992, 48, 10075, which discuss reductive aminations of relevance to the present invention, and in Salvino et. al. J. Org. Chem. 1999, 64, 1823 and Floyd et. al. Tetrahedron Lett. 1996, 37, 8045-8048 which both describe suitably modified resins. However, none of these procedures have been employed for the multi-step parallel

preparation of tertiary amines, which is the subject matter disclosed in the present application.

Analysis of reaction products was performed using LC-MS and NMR spectroscopy. For LC-MS analyses, a HP 1100 LC-MSD system equipped with a binary pump and diode array detector was used. Mass spectral data were collected using an electrospray interface at positive mode, scanning from mass 80 to mass 700. The column was a Luna C18, 3 micrometer particle size, measuring 4.6x75 mm. A Phenomenex C18 4x3 mm guard column was used. The mobile phase consisted of A: 50% 8mM ammoniumacetate / 50% acetonitrile and B: 5% 8 mM ammoniumacetate / 95% acetonitrile. A gradient program: 44.5% B at time 0 min increasing linearly to 100% B at time 11 min was used. The flowrate was 0.6 ml/min. Rt indicates retention times for the products under these experimental condition. NMR spectra were recorded on a 400 MHz apparatus.

Solution phase experiments (P = benzyl):

Example 1: Step (a), introduction of (Alk^1)

Synthesis of O-(Benzyl)benzaldoxime(I)

A solution of O-(benzyl)hydroxylamine (1 eq.), benzaldehyde (1 eq.) and acetic acid (5% v/v in MeOH) was stirred for 15 h at rt. Aqueous workup and column chromatography gave I as a colorless oil. The product was identified using NMR spectroscopy, e.g. a peak at 8.18ppm (singlet, HC=N) was diagnostic.

Example 2: Step (b), introduction of (Alk^1)

Synthesis of N-Benzyl-O-(benzyl)hydroxylamine (II)

To a solution of I (1eq.) and BH_3(pyridine) (4 eq.) in methanol was added HCl in dioxane (excess). The reaction mixture was stirred at rt for 12 h. Aqueous basic workup and column chromatography afforded II as a colorless oil. LC-MS: Rt = 5.1 min.

Example 3: Step (c), introduction of (Alk^2)

Synthesis of N-Isobutyl-N,O-dibenzylhydroxylamine (III)

To a solution of II (1 eq.), 2-methylpropanal (1 eq.) and BH_3(pyridine) (1 eq.) in THF:MeOH (1:3) was added PPTS (1eq.). The reaction mixture was stirred at rt for 12 h and afforded, after aqueous workup and purification by column chromatography, III as a colorless oil.

LC-MS: Rt = 11.3 min.

Example 4: Step (d), introduction of (R")

Quaternization of III to give IV

To a solution of III (1 eq.) in CH_2Cl_2 was added Na_2CO_3 (excess) and MeOTf (5 eq.). The reaction mixture was stirred at rt for 15 h. Evaporation of excess MeOTf and CH_2Cl_2 afforded a mixture of Na_2CO_3 and IV. Extraction with EtOH afforded the product as a white solid after evaporation.

Analysis by NMR confirmed the identity of the product, e. g. a diagnostic peak at 3.6 ppm (singlet, N^+Me)

Similar reactions excluding Na_2CO_3 were also effective.

Example 5: Step (e), cleavage

Synthesis of N-Benzyl-N-isobutyl-N-methylamine (V)

To a solution of IV in dioxane or MeCN was added LiI (2 eq.). The reaction mixture was heated for 12 h at 70° C. Aqueous workup and purification through an ion exchange column (Isolute SCX) afforded V. LC-MS: Rt = 5.8 min.

Similar cleavages of compound IV were effected using Et_3N in CH_2Cl_2, K_2CO_3 in DMF or SmI_2 in THF.

Solid phase experiments (P = solid support):

Synthesis of a hydroxylamine substrate $PONH_2$ (P = solid support) from Argogel resin was conducted in analogy with the procedure in Salvino et. al. J. Org. Chem. 1999, 64, 1823, which provided the required polystyrene-polyethylene glycol-ONH_2 resin (VI).

Example 6: Step (a), introduction of (Alk^1)

Oxime resin (VII)

Resin VI was swollen in THF:MeOH (2:1) for 5 min. Cyclohexylcarboxaldehyde (excess) and HOAc were added. The mixture was stirred at rt for 150 h. The resin was filtered and washed with THF and MeOH followed by drying at 40 °C under vacuo.

Example 7: Step (a), introduction of (Alk^1)

Hydroxylamine resin (VIII)

To oxime resin VII in THF:MeOH (1:1) were added BH_3(pyridine) and HCl in dioxane (both in excess). The reaction mixture was shaken at rt for 15 h, filtered and washed with Et_3N in MeOH and then MeOH and finally dried in vacuo

Example 8: Step (b), introduction of (Alk^2)

Hydroxylamine resin (IX)

To resin VIII in THF:MeOH (3:1) was added 2-methylpropanal (excess), BH_3(pyridine) (excess) and PPTS (excess). The reaction mixture was shaken at rt for 12 h, filtered and washed with MeOH and THF followed by drying under vacuo.

Example 9: Step (c), introduction of (R")

Quaternization of hydroxylamine resin IX

To resin IX in CH_2Cl_2 was added MeOTf (excess). The reaction mixture was shaken at rt for 12 h, filtered, washed with CH_2Cl_2 and dried under vacuo to provide the quaternized resin X.

Example 10: Step (d), cleavage

Preparation of N-Cyclohexylmethyl-N-isobutyl-N-methylamine

Quaternized resin X, prepared above, when subjected to any of the conditions given in Example 5 above, released the desired amine, N-Cyclohexylmethyl-N-isobutyl-N-methylamine.

We claim

1. A method for preparing tertiary amines comprising:

sequential, exhaustive alkylation of a hydroxylamine derivative; and,

cleavage of the O-N bond.

2. The method of claim 1 wherein the sequential, exhaustive alkylation of a hydroxylamine derivative of the formula $PONH_2$ comprises the steps of:

a) forming an alkylated derivative, having the formula $PONH(Alk^{1)}$, by reacting the hydroxylamine derivative with

an alkylating agent having the formula R-X,

or a carbonyl compound having the formula RCOR' to form an oxime intermediate having the formula PON=CR'R and reacting the oxime intermediate with a reducing agent;

b) forming a dialkylated derivative having the formula $PON(Alk^1)(Alk^2)$ by reacting the alkylated derivative with

an alkylating agent having the formula R-LG,

or a carbonyl compound having the formula RCOR' in the presence of a reducing agent; and,

c) reacting the dialkylated derivative with an alkylating agent having the formula R"-X' to produce a quaternized derivative, having the formula $PON^+R"(Alk^1)(Alk^2)$, wherein P is an organyl group or solid support, R is an organyl group, R' is an organyl group or hydrogen, R" is an organyl group, X and X' are each a nucleofuge, and Alk^1 and

Alk^2 are the same or different and are each independently selected from the group consisting of R and CHRR'.

3. The method of claim 2 wherein P is a solid support.

4. The method of claim 2 wherein P is grafted or functionalized polystyrene.

5. The method of claim 2 wherein P is selected from the group consisting of Wang resin, Argogel resin, Merrifield resin and Tentagel resin.

6. The method of claim 2, wherein P is benzyl.

7. The method of claim 2 wherein the alkylating agents are selected from the group consisting of primary organyl chloride, bromide, iodide, tosylate, mesylate and triflate.

8. The method of claim 2 wherein the reducing agent is a complex hydride reagent.

9. The method of claim 8 wherein the reducing agent is applied under acidic conditions.

10. The method of claim 2 wherein the reducing agent is selected from the group consisting of BH_3(pyridine), $NaCNBH_3$, $NaBH_4$, $Na(OAc)_3BH$, $Zn(BH_4)_2$, and B_2H_6.

11. The method of claim 2 where X is triflate.

12. The method of claim 2 wherein step b) is performed using a carbonyl compound and wherein the carbonyl compound is an aldehyde or ketone.

13. The method of claim 2 wherein step d) is performed using a bifunctional reagent, such that R" and (Alk^2) of the quaternized derivative form a ring.

14. The method of claim 13 wherein the ring contains 4, 5, or 6 carbon atoms.

15. The method described in claim 1, wherein the sequential, exhaustive alkylation of a hydroxylamine derivative produces a quaternized derivative having the formula $PON^{+}R"(Alk^1)(Alk^2)$, and wherein cleavage of the O-N bond comprises reacting the quaternized derivative with a reagent causing cleavage of the O-N bond to produce a tertiary amine having the formula $NR"(Alk^1)(Alk^2)$ where R" is an organyl and Alk^1 and Alk^2 are the same or different and are each independently selected from the group consisting of R and CHRR'.

16. The method of claim 15 wherein the reagent is iodide ion or a base.

17. The method of claim 15 wherein the reagent is samarium iodide or lithium iodide.

18. The method of claim 15 wherein the reagent is a trialkyl amine or carbonate.

19. A method for preparing tertiary amines comprising:

a) forming an alkylated derivative, having the formula $PONH(Alk^{1)}$, by reacting the hydroxylamine derivative with

an alkylating agent having the formula R-X,

or a carbonyl compound having the formula RCOR' to form an oxime intermediate having the formula PON=CR'R and reacting the oxime intermediate with a reducing agent;

b) forming a dialkylated derivative having the formula $PON(Alk^1)(Alk^2)$ by reacting the alkylated derivative with

an alkylating agent having the formula R-LG,

or a carbonyl compound having the formula RCOR' in the presence of a reducing agent; and,

c) reacting the dialkylated derivative with an alkylating agent having the formula R"-X' to produce a quaternized derivative, having the formula $PON^+R"(Alk^1)(Alk^2)$; and,

d) reacting the quaternized derivative with a reagent causing cleavage of the O-N bond to produce a tertiary amine having the formula $NR"(Alk^1)(Alk^2)$;

wherein P is an organyl group or solid support, R is an organyl group, R' is an organyl group or hydrogen, R" is an organyl group, X and X' are the same or different and are each a nucleofuge, and Alk^1 and Alk^2 are the same or different and are each independently selected from the group consisting of R and CHRR'.

20. The method of claim 19 wherein P is grafted or functionalized polystyrene, the hydroxylamine derivative is reacted with a carbonyl compound and the alkylated derivative is reacted with a carbonyl compound, the reducing agent is BH_3(pyridine), $NaCNBH_3$, or $Na(OAc)_3BH$, R" is a methyl group, X is triflate, and the reagent is iodide ion or a base.

21. The method of claim 19 wherein P is a solid support.

22. The method of claim 19 wherein P is grafted or functionalized polystyrene.

23. The method of claim 19 wherein P is selected from the group consisting of Wang resin, Argogel resin, Merrifield resin and Tentagel resin.

24. The method of claim 19 wherein P is benzyl.

25. The method of claim 19 wherein the alkylating agents are selected from the group consisting of primary organyl chloride, bromide, iodide, tosylate, mesylate and triflate.

26. The method of claim 19 wherein the reducing agent is a complex hydride reagent.

27. The method of claim 26 wherein the reducing agent is applied under acidic conditions.

28. The method of claim 19 wherein the reducing agent is selected from the group consisting of BH_3(pyridine), $NaCNBH_3$, $NaBH_4$, $Na(OAc)_3BH$, $Zn(BH_4)_2$, and B_2H_6.

29. The method of claim 19 where X is triflate.

30. The method of claim 19 wherein step d) is performed using a bifunctional reagent, such that R" and (Alk^2) of the quaternized derivative form a ring.

31. The method of claim 30 wherein the ring contains 4, 5, or 6 carbon atoms.

32. The method of claim 19 wherein the reagent is iodide ion or a base.

33. The method of claim 19 wherein the reagent is samarium iodide or lithium iodide.

34. The method of claim 19 wherein the reagent is a trialkyl amine or carbonate.

Abstract

Described is method for preparing tertiary amines comprising sequential, exhaustive alkylation of a hydroxylamine derivative and cleavage of the O-N bond using the following steps:

a) reacting the hydroxylamine derivative with an alkylating agent or with a carbonyl compound to form an oxime intermediate.

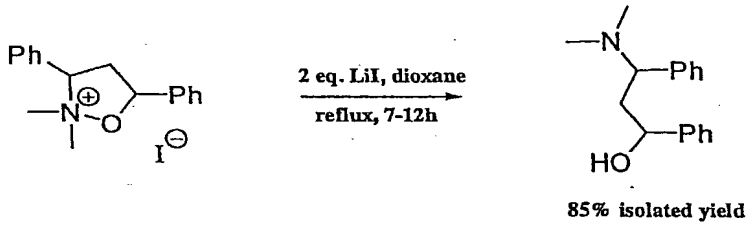
b) reacting the oxime intermediate with a reducing agent to produce an alkylated derivative

c) reacting the alkylated derivative with an alkylating agent or a carbonyl compound in the presence of a reducing agent to produce a dialkylated derivative

d) reacting the dialkylated derivative with an alkylating agent to produce a quaternized derivative

e) reacting the quaternized derivative with a reagent causing cleavage of the O-N bond to produce a tertiary amine.

Figure 1



85% isolated yield

Figure 2

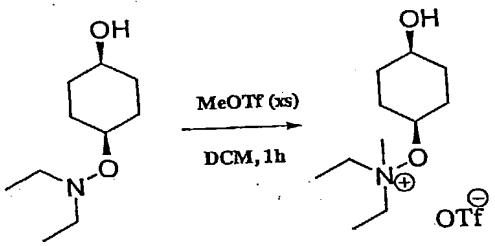


Fig 2a

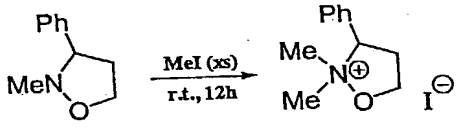


Fig 2b

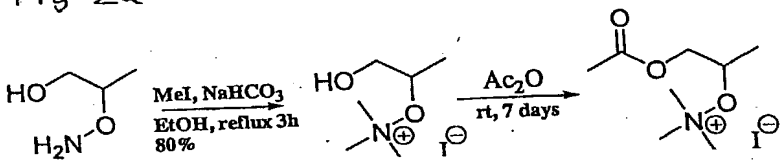


Fig 2c

Figure 3

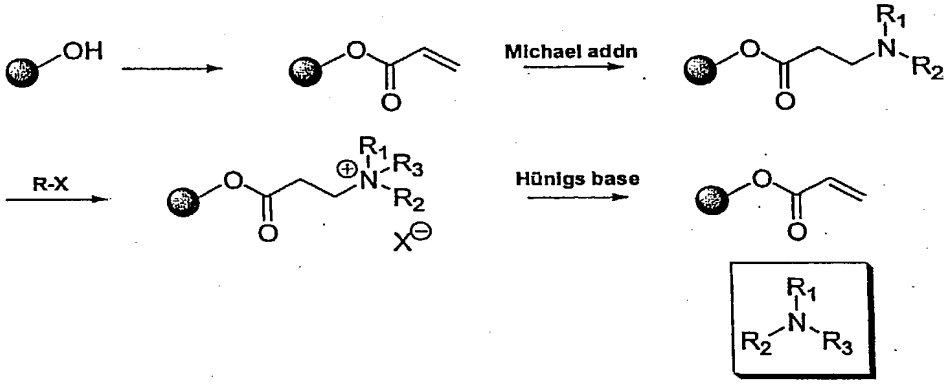


Figure 4

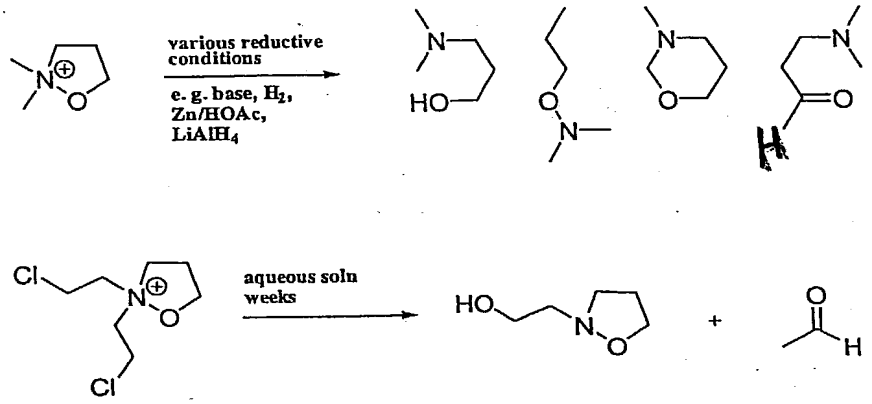


Figure 5

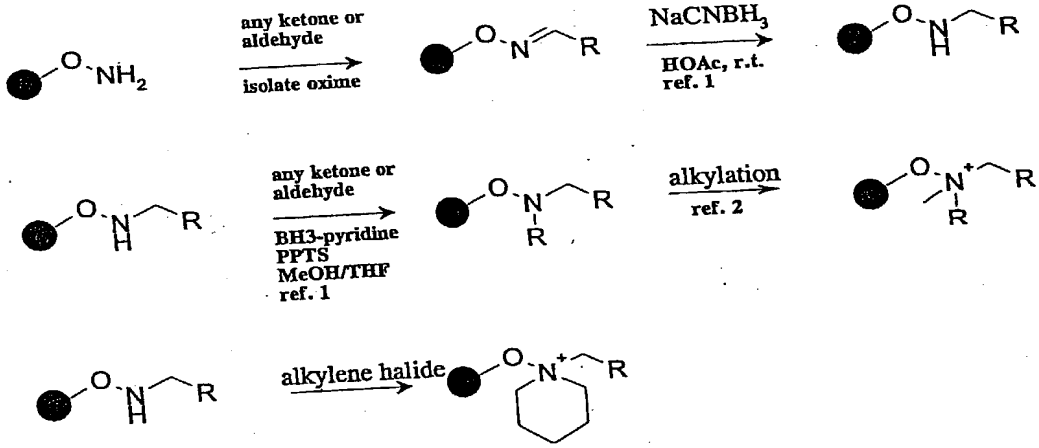


Figure 6

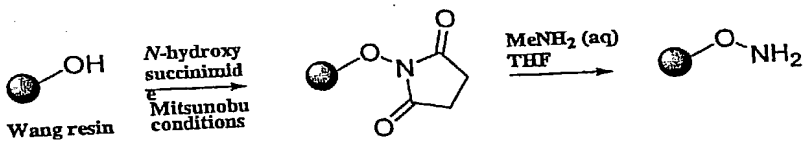


Figure 7

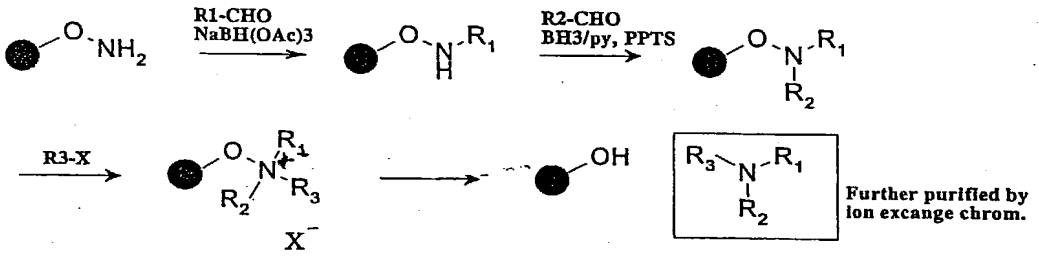
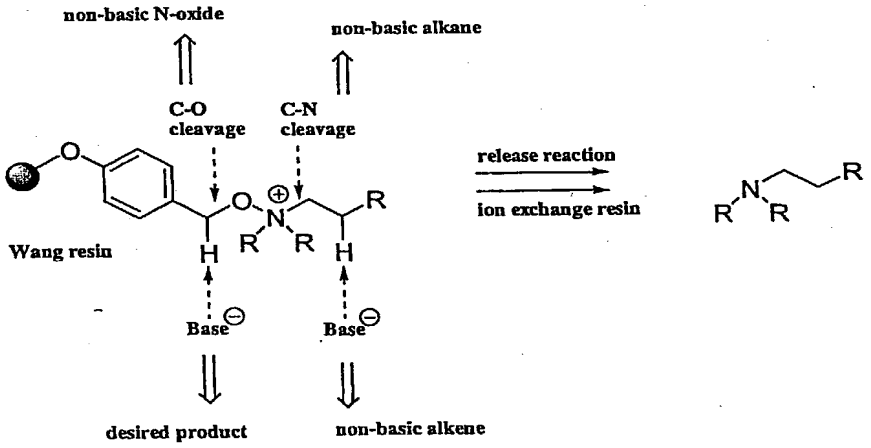


Figure 8



DECLARATION AND POWER OF ATTORNEY- USA PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled SOLID PHASE PARALLEL SYNTHESIS OF TERTIARY AMINES; the specification of which was filed on **February 12, 2002** as Application Serial No. **10/049,669**.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above;

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56;

I hereby claim the benefit under Title 35, United States Codes § 119(e) of any United States provisional application(s) listed below.

Application No.: 60/146,978 Filing Date: August 3, 1999

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN APPLICATION(S)			Priority Claimed
No.: **PCT/US00/21225**	Country: **PCT**	Date Filed: **08/03/00**	**Yes**

POWER OF ATTORNEY: I hereby appoint the registrants of Knobbe, Martens, Olson & Bear, LLP, 2040 Main Street, 14th Floor, Irvine, California 92614, Telephone (949) 760-0404, **Customer No. 20,995**.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

Full name of first inventor: **Carl-Magnus A. Andersson**

Inventor's signature

Date 05NOV02

Residence: **Dahlvangvej 81.2 MF, DK-2600, Glostrup, Denmark**

Citizenship: **Sweden** DKX

Post Office Address: **Dahlvangvej 81.2 MF, DK-2600, Glostrup, Denmark**

2-00

Full name of second inventor: **Magnus Gustafsson**

Inventor's signature

Date 30/10 - 2002

Residence: **Kung Oskars vag 9A, 22240 Lund, Sweden** SEX

Citizenship: **Sweden**

Post Office Address: **Kung Oskars vag 9A, 22240 Lund, Sweden**

3-00

Full name of third inventor: **Kent R.I. Olsson**

Inventor's signature

Date 30/10 - 2002

Residence: **Andreegatan 8, 211 49, Malmo, Sweden** SEX

Citizenship: **Sweden**

Post Office Address: **Andreegatan 8, 211 49, Malmo, Sweden**

Send Correspondence To:
KNOBBE, MARTENS, OLSON & BEAR, LLP
Customer No. 20,995

ACADIA.024NP

10/049669

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Andersson, et al.
App. No.	:	10/049,669
Filed	:	February 12, 2002
For	:	SOLID PHASE PARALLEL SYNTHESIS OF TERTIARY AMINES
Examiner	:	Unknown

ESTABLISHMENT OF RIGHT OF ASSIGNEE TO TAKE ACTION
AND
REVOCATION AND POWER OF ATTORNEY

United States Patent and Trademark Office
P.O. Box 2327
Arlington, VA 22202

Dear Sir:

The undersigned is empowered to act on behalf of the assignee below (the "Assignee"). A true copy of the original Assignment of the above-captioned application from the inventor(s) to the Assignee is attached hereto. This Assignment represents the entire chain of title of this invention from the Inventor(s) to the Assignee.

I declare that all statements made herein are true, and that all statements made upon information and belief are believed to be true, and further, that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that willful, false statements may jeopardize the validity of the application, or any patent issuing thereon.

The undersigned hereby revokes any previous powers of attorney in the subject application, and hereby appoints the registrants of Knobbe, Martens, Olson & Bear, LLP, 2040 Main Street, Fourteenth Floor, Irvine, California 92614, Telephone (949) 760-0404, **Customer**

App. No. : 10/049,669
Filed : February 12, 2002

No. 20,995, as its attorneys with full power of substitution and revocation to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected herewith. This appointment is to be to the exclusion of the inventor(s) and his attorney(s) in accordance with the provisions of 37 C.F.R. § 3.71.

Please use **Customer No. 20,995** for all communications.

ACADIA PHARMACEUTICALS, INC.

Dated: October 25, 2002

By: Uli Hacksell
Uli Hacksell, Ph.D.

Title: CEO and Director

Address: 3911 Sorrento Valley Blvd.
San Diego, CA 92121

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- DO NOT RECORD -

Application No.: 10/049,669
Filing Date: February 12, 2002

PATENT
Client Code: ACADIA.024NP
Page 1

ASSIGNMENT

WHEREAS, We, Carl-Magnus A. Andersson, a Swedish citizen, residing at Dahlvangvej 81.2 MF, DK-2600, Glostrup, Denmark; Magnus Gustafsson, a Swedish citizen, residing at Kung Oskars vag 9A, 22240 Lund, Sweden; and Kent R.I. Olsson, a Swedish citizen, residing at Andreegatan 8, 211 49 Malmo, Sweden, have invented certain new and useful improvements in a SOLD PHASE PARALLEL SYNTHESIS OF TERTIARY AMINES for which we have filed an application for Letters Patent in the United States, Application No. 10/049,669, Filing Date February 12, 2002;

AND WHEREAS, Acadia Pharmaceuticals, Inc. (hereinafter "ASSIGNEE"), a Delaware Corporation, with its principal place of business at 3911 Sorrento Valley Boulevard, San Diego, California 92121, desires to acquire the entire right, title, and interest in and to the said improvements and the said Application:

NOW, THEREFORE, in consideration of the sum of One Dollar ($1.00) to me in hand paid, and other good and valuable consideration, the receipt of which is hereby acknowledged, we, the said inventors, do hereby acknowledge that we have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over, unto the said ASSIGNEE, its successors, legal representatives and assigns, the entire right, title, and interest throughout the world in, to and under the said improvements, and the said application and all provisional applications relating thereto, and all divisions, renewals and continuations thereof, and all Letters Patent of the United States which may be granted thereon and all reissues and extensions thereof, and all rights of priority under International Conventions and applications for Letters Patent which may hereafter be filed for said improvements in any country or countries foreign to the United States, and all Letters Patent which may be granted for said improvements in any country or countries foreign to the United States and all extensions, renewals and reissues thereof; and we hereby authorize and request the Commissioner of Patents of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all Letters Patent for said improvements to the said ASSIGNEE, its successors, legal representatives and assigns, in accordance with the terms of this instrument.

AND WE HEREBY covenant and agree that we will communicate to the said ASSIGNEE, its successors, legal representatives and assigns, any facts known to us respecting said improvements, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuing and reissue applications, make all rightful oaths and generally do everything possible to aid the said ASSIGNEE, its successors, legal representatives and assigns, to obtain and enforce proper patent protection for said improvements in all countries.

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 5th day of November, 2002.

Carl-Magnus A. Andersson

STATE OF)
) ss.
COUNTY OF)

On _____, before me, _____, personally appeared Carl-Magnus A. Andersson personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity(ies), and that by his signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

[SEAL]

_____
Notary Signature

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 30 day of October, 2002.

Magnus Gustafsson

STATE OF)
) ss.
COUNTY OF)

On _____, before me, _____, personally appeared Magnus Gustafsson personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity(ies), and that by his signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

[SEAL]

Notary Signature

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 30 day of October, 2002.

Kent Roger I. Olsson

STATE OF)
) ss.
COUNTY OF)

On _____, before me, _____, personally appeared Kent Roger I. Olsson personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity(ies), and that by his signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

[SEAL]

Notary Signature